Abstracts of Articles

Draghici S.
The constraint based decomposition (CBD) training architecture.
**Neural Netw. 2001 May; 14(4-5):527-50.**
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The Constraint Based Decomposition (CBD) is a constructive neural network technique that builds a three or four layer network, has guaranteed convergence and can deal with binary, n-ary, class labeled and real-value problems. CBD is shown to be able to solve complicated problems in a simple, fast and reliable manner. The technique is further enhanced by two modifications (locking detection and redundancy elimination) which address the training speed and the efficiency of the internal representation built by the network. The redundancy elimination aims at building more compact architectures while the locking detection aims at improving the training speed. The computational cost of the redundancy elimination is negligible and this enhancement can be used for any problem. However, the computational cost of the locking detection is exponential in the number of dimensions and should only be used in low dimensional spaces. The experimental results show the performance of the algorithm presented in a series of classical benchmark problems including the 2-spiral problem and the Iris, Wine, Glass, Lenses, Ionosphere, Lung cancer, Pima Indians, Bupa, TicTacToe, Balance and Zoo data sets from the UCI machine learning repository. CBD's generalization accuracy is compared with that of C4.5, C4.5 with rules, incremental decision trees, oblique classifiers, linear machine decision trees, CN2, learning vector quantization (LVQ), backpropagation, nearest neighbor, Q* and radial basis functions (RBFs). CBD provides the second best average accuracy on the problems tested as well as the best reliability (the lowest standard deviation).

Hunt T.
Bright and dynamic, constantly updated and enhanced online.?
**J Cell Sci. 2000;113(Pt 24):4377-4378.**
ICRF Clare Hall Laboratories, South Mimms, Herts, UK.

Nature Reviews Molecular Cell Biology Nature Publishing Group (2000). ISSN 1471-0072. Monthly First there was Annual Reviews, then came the monthly Elsevier Trends Journals, both of which try to identify hot topics in their chosen fields. The Current Opinion journals followed several years later, and Current Opinion in Cell Biology is presently one of the highest 'impact factor' review journals, with a distinguished board of editors and advisors and a systematic approach to regular coverage of the major fields of cell biology. Important topics are visited once a year, whether or not something specially exciting happened in the last 12 months. Add to this list Seminars in Cell and Developmental Biology, the FASEB journal and the countless minireviews in 'real' journals, and you begin to wonder how anyone finds any time for doing experiments, or indeed reading the primary literature. So, into this already crowded field arrive three

important newcomers: Nature Reviews in Molecular Cell Biology, Genetics, and Neurosciences, of which the first two will probably interest readers of Journal of Cell Science the most. Backed by the name and money of Nature and edited by experienced Nature staff, it is hard to see how these publications can possibly do other than succeed with writers and readers alike. What's inside the first issue? The cover of Nature Reviews in Molecular Cell Biology presents a 3-colour montage of a blue cell nucleus surrounded by splotches of green GPI-anchored GFP overlaid by orange actin stress fibres that seem to come from somewhere else. This image trails a comprehensive review from Kai Simons and Derek Toomre about Lipid Rafts. There are another five major review articles: calcium puffs and sparks, rings around DNA, HIV inhibitors, kinesin and the circadian clock provide a rich and varied mix of topics from authors who know what they're talking about. Surrounding this core is an entertaining mixture of 'highlights' at the front: news and views about a well-chosen selection of recent articles in the primary literature written by the three editors. These struck me as striking slightly too jokey a style. It is a terrible temptation and mistake in this kind of piece, I think, to equate lightheartedness with clarity. The sugar coating is more likely to irritate than enlighten. I would also question the wisdom, if it is indeed a policy, of only allowing editors to write in this section. I'm all for experienced writers writing, but I think I would prefer the variety of voice and authority evinced by the parental Nature News and Views. After the main reviews comes a section entitled 'perspectives', which include a 'Timeline' piece on Hayflick and his limit by Jerry Shay and Woodring Wright that I very much enjoyed, and a review (or Opinion) about cancer from Judah Folkman, Philip Hahnfeldt and Lynn Hlatky. In their own words, "the impetus for this Opinion article centres on the increasing awareness of the heterogeneity and instability of the cancer genome [. I]t is possible that suppressing this degenerative process may itself comprise an alternative constraint-based paradigm." The authors' fondness for portentous phrases of this kind rather spoiled their discussion for me. I also had trouble with an article on molecular computing. PCR reactions can solve the travelling salesman problem, it seems, but extremely slowly compared to a proper computer. The magazine has a nice heft to it, and is attractively designed and presented in glossy colour, although the main font is small enough to make reading difficult for your middle-aged reviewer in a particularly heavily overcast and rainy week in London. A first issue is supposed to be a kind of showcase, but if they can keep this up, the editors will surely have a success on their hands and you will probably be obliged to take out a personal subscription (Â£85), or persuade your library to part with Â£565. That's slightly cheaper than TiBS and a lot cheaper than Current Opinion in Cell Biology, both of which will have to run faster if they want to stay in the same place.

Aluvihare V V.
Nature's loss, Immunologists gain?
**J Cell Sci. 2000;113(Pt 24):4377-4378.**
Wellcome Trust Immunology Unit, Addenbrooke's site, Cambridge, UK.

Nature Reviews Molecular Cell Biology Nature Publishing Group (2000). ISSN 1471-0072. Monthly First there was Annual Reviews, then came the monthly Elsevier Trends Journals, both of which try to identify hot topics in their chosen fields. The Current Opinion journals followed several years later, and Current Opinion in Cell Biology is

presently one of the highest 'impact factor' review journals, with a distinguished board of editors and advisors and a systematic approach to regular coverage of the major fields of cell biology. Important topics are visited once a year, whether or not something specially exciting happened in the last 12 months. Add to this list Seminars in Cell and Developmental Biology, the FASEB journal and the countless minireviews in 'real' journals, and you begin to wonder how anyone finds any time for doing experiments, or indeed reading the primary literature. So, into this already crowded field arrive three important newcomers: Nature Reviews in Molecular Cell Biology, Genetics, and Neurosciences, of which the first two will probably interest readers of Journal of Cell Science the most. Backed by the name and money of Nature and edited by experienced Nature staff, it is hard to see how these publications can possibly do other than succeed with writers and readers alike. What's inside the first issue? The cover of Nature Reviews in Molecular Cell Biology presents a 3-colour montage of a blue cell nucleus surrounded by splotches of green GPI-anchored GFP overlaid by orange actin stress fibres that seem to come from somewhere else. This image trails a comprehensive review from Kai Simons and Derek Toomre about Lipid Rafts. There are another five major review articles: calcium puffs and sparks, rings around DNA, HIV inhibitors, kinesin and the circadian clock provide a rich and varied mix of topics from authors who know what they're talking about. Surrounding this core is an entertaining mixture of 'highlights' at the front: news and views about a well-chosen selection of recent articles in the primary literature written by the three editors. These struck me as striking slightly too jokey a style. It is a terrible temptation and mistake in this kind of piece, I think, to equate lightheartedness with clarity. The sugar coating is more likely to irritate than enlighten. I would also question the wisdom, if it is indeed a policy, of only allowing editors to write in this section. I'm all for experienced writers writing, but I think I would prefer the variety of voice and authority evinced by the parental Nature News and Views. After the main reviews comes a section entitled 'perspectives', which include a 'Timeline' piece on Hayflick and his limit by Jerry Shay and Woodring Wright that I very much enjoyed, and a review (or Opinion) about cancer from Judah Folkman, Philip Hahnfeldt and Lynn Hlatky. In their own words, "the impetus for this Opinion article centres on the increasing awareness of the heterogeneity and instability of the cancer genome [. I]t is possible that suppressing this degenerative process may itself comprise an alternative constraint-based paradigm." The authors' fondness for portentous phrases of this kind rather spoiled their discussion for me. I also had trouble with an article on molecular computing. PCR reactions can solve the travelling salesman problem, it seems, but extremely slowly compared to a proper computer. The magazine has a nice heft to it, and is attractively designed and presented in glossy colour, although the main font is small enough to make reading difficult for your middle-aged reviewer in a particularly heavily overcast and rainy week in London. A first issue is supposed to be a kind of showcase, but if they can keep this up, the editors will surely have a success on their hands and you will probably be obliged to take out a personal subscription (Â£85), or persuade your library to part with Â£565. That's slightly cheaper than TiBS and a lot cheaper than Current Opinion in Cell Biology, both of which will have to run faster if they want to stay in the same place.

Schilling CH, Covert MW, Famili I, Church GM, Edwards JS, Palsson BO.
Genome-scale metabolic model of Helicobacter pylori 26695.
**J Bacteriol. 2002 Aug; 184(16):4582-93.**

Genomatica, Inc., San Diego, California 92121, USA. cschilling@genomatica.com
A genome-scale metabolic model of Helicobacter pylori 26695 was constructed from genome sequence annotation, biochemical, and physiological data. This represents an in silico model largely derived from genomic information for an organism for which there is substantially less biochemical information available relative to previously modeled organisms such as Escherichia coli. The reconstructed metabolic network contains 388 enzymatic and transport reactions and accounts for 291 open reading frames. Within the paradigm of constraint-based modeling, extreme-pathway analysis and flux balance analysis were used to explore the metabolic capabilities of the in silico model. General network properties were analyzed and compared to similar results previously generated for Haemophilus influenzae. A minimal medium required by the model to generate required biomass constituents was calculated, indicating the requirement of eight amino acids, six of which correspond to essential human amino acids. In addition a list of potential substrates capable of fulfilling the bulk carbon requirements of H. pylori were identified. A deletion study was performed wherein reactions and associated genes in central metabolism were deleted and their effects were simulated under a variety of substrate availability conditions, yielding a number of reactions that are deemed essential. Deletion results were compared to recently published in vitro essentiality determinations for 17 genes. The in silico model accurately predicted 10 of 17 deletion cases, with partial support for additional cases. Collectively, the results presented herein suggest an effective strategy of combining in silico modeling with experimental technologies to enhance biological discovery for less characterized organisms and their genomes.

Matsuda T, Suzuki H, Oishi I, Kani S, Kuroda Y, Komori T, Sasaki A, Watanabe K, Minami Y.
The receptor tyrosine kinase Ror2 associates with the MAGE-family protein Dlxin-1 and regulates its intracellular distribution.
**J Biol Chem. 2003 May 16 [epub ahead of print]**
Department of Genome Sciences, Faculty of Medical Sciences, Graduate School of Medicine, Kobe University, Kobe 650-0017, Japan.

The mammalian Ror family receptor tyrosine kinases, Ror1 and Ror2, play crucial roles in developmental morphogenesis. Although the functions of Ror1 and Ror2 are redundant, Ror2 exhibits more specific functions during development. We show that when expressed in mammalian cells, Ror2, but not Ror1, associates with the melanoma-associated antigen (MAGE) family protein, Dlxin-1, which is known to bind to the homeodomain proteins Msx2 and Dlx5 and regulate their transcriptional functions. This association requires the cytoplasmic C-terminal region of Ror2, containing proline-rich and serine/threonine-rich domains, and the C-terminal necdin homology domain of Dlxin-1. Interestingly, the cytoplasmic C-terminal region of Ror2 is missing in patients with brachydactyly type B. Interestingly, transient expression and immunohistochemical analyses reveal that both Dlxin-1 and Msx2 are co-localized in the nuclei in the absence of Ror2. In the presence of Ror2, Dlxin-1 is co-localized with Ror2 at the membranous compartments and Msx2 is retained in the nuclei. It was also found that the majority of cellular Dlxin-1 is retained in the membrane fractions of wild-type but not Ror2-/- mouse embryonic fibroblasts. Furthermore, we show that transcriptional activity of Msx2,

irrespective of Ror2 kinase activity, is regulated by ectopic expression of Ror2 using a reporter plasmid containing the WIP element. Thus, Ror2 sequesters Dlxin-1 in membranous compartments, thereby affecting the transcriptional function of Msx2.

Yoda A, Oishi I, Minami Y.
Expression and function of the Ror-family receptor tyrosine kinases during development: lessons from genetic analyses of nematodes, mice, and humans.
**J Recept Signal Transduct Res. 2003 Feb; 23(1):1-15.**
Department of Genome Sciences, Graduate School of Medicine, Kobe University, Kobe, Japan.

Receptor tyrosine kinases (RTKs) play crucial roles in various developmental processes. Ror-family RTKs are characterized by the intracellular tyrosine kinase domains, highly related to those of the Trk-family RTKs, and by the extracellular Frizzled-like cysteine-rich domains (CRDs) and Kringle domains. Rors are evolutionally conserved among Caenorhabditis elegans, Aplysia, Drosophila melanogaster, Xenopus, mice, and humans. In D. melanogaster and mammals, pairs of structurally related Rors are found, while a single Ror protein is identified in C. elegans or Aplysia. In Aplysia and D. melanogaster, Rors are expressed exclusively in developing nervous systems. On the other hand, rather widespread expression of Rors was observed in C. elegans and mammals. Mutations in Ror of C. elegans cause inappropriate axon outgrowth as well as defects in cell migration and asymmetric cell division. It has also been reported that the nematode Ror possesses kinase-dependent and kinase-independent functions. Mouse Rors, Ror1, and Ror2, are expressed mainly in migrating neural crest cells and mesenchymal cells, and Ror2-deficient mice exhibit skeletal abnormalities and ventricular septal defects in the heart. Although Ror1-deficient mice exhibit no apparent skeletal or cardiac abnormalities, Ror1/Ror2 double mutant mice show markedly enhanced skeletal and cardiac abnormalities compared with Ror2 mutant mice, indicating genetic interaction of Ror1 and Ror2. In humans, mutations within Ror2 have been found in two genetic skeletal disorders, recessive Robinow syndrome and dominant Brachydactyly type B (BDB), further emphasizing critical functions of Ror2 during developmental morphogenesis. In this article, we also discuss the signaling machinery mediated by Ror-family RTKs with a particular emphasis on our recent structure-function analyses of Ror-family RTKs.

Freialdenhoven A, Peterhansel C, Kurth J, Kreuzaler F, Schulze-Lefert P.
Identification of Genes Required for the Function of Non-Race-Specific mlo Resistance to Powdery Mildew in Barley.
**Plant Cell. 1996 Jan; 8(1):5-14.**
Rheinisch-Westfalische Technische Hochschule Aachen, Department of Biology I, Worringer Weg 1, D-52074 Aachen, Germany.

Recessive alleles (mlo) of the Mlo locus in barley mediate a broad, non-race-specific resistance reaction to the powdery mildew fungus Erysiphe graminis f sp hordei. A

mutational approach was used to identify genes that are required for the function of mlo. Six susceptible M2 individuals were isolated after inoculation with the fungal isolate K1 from chemically mutagenized seed carrying the mlo-5 allele. Susceptibility in each of these individuals is due to monogenic, recessively inherited mutations in loci unlinked to mlo. The mutants identify two unlinked complementation groups, designated Ror1 and Ror2 (required for mlo-specified resistance). Both Ror genes are required for the function of different tested mlo alleles and for mlo function after challenge with different isolates of E. g. f sp hordei. A quantitative cytological time course analysis revealed that the host cell penetration efficiency in the mutants is intermediate compared with mlo-resistant and Mlo-susceptible genotypes. Ror1 and Ror2 mutants could be differentiated from each other by the same criterion. The spontaneous formation of cell wall appositions in mlo plants, a subcellular structure believed to represent part of the mlo defense, is suppressed in mlo/ror genotypes. In contrast, accumulation of major structural components in the appositions is seemingly unaltered. We conclude that there is a regulatory function for the Ror genes in mlo-specified resistance and propose a model in which the Mlo wild-type allele functions as a negative regulator and the Ror genes act as positive regulators of a non-race-specific resistance response.

Peterhansel C, Freialdenhoven A, Kurth J, Kolsch R, Schulze-Lefert P.
Interaction Analyses of Genes Required for Resistance Responses to Powdery Mildew in Barley Reveal Distinct Pathways Leading to Leaf Cell Death.
**Plant Cell. 1997 Aug; 9(8):1397-1409.**
Rheinisch-Westfalische Technische Hochschule Aachen, Department of Biology I, Worringer Weg 1, D-52074 Aachen, Germany.

Race-specific resistance in barley to the powdery mildew fungus (Erysiphe graminis f sp hordei) is associated with a cell death reaction (hypersensitive response [HR]). Genetically, it is dependent on dominant resistance genes (Mlx), and in most cases, it is also dependent on Rar1 and Rar2. Non-race-specific resistance to the fungus, which is due to the lack of the Mlo wild-type allele, is dependent on Ror1 and Ror2 and is not associated with an HR in the region of pathogen attack. However, the absence of the Mlo wild-type allele stimulates a spontaneous cell death response in foliar tissue. This response is also controlled by Ror1 and Ror2, as indicated by trypan blue staining patterns. Lack of Mlo enhances transcript accumulation of pathogenesis-related genes upon fungal challenge, and this response is diminished by mutations in Ror genes. Using DNA marker-assisted selection of genotypes, we provide evidence, via gene interaction studies, that Ror1 and Ror2 are not essential components of race-specific resistance and do not compromise hypersensitive cell death. Reciprocal experiments show that neither is Rar1 a component of mlo-controlled resistance nor does it affect spontaneous cell death. We show that mlo- and Ror-dependent resistance is active when challenged with E. g. f sp tritici, a nonhost pathogen of barley. Our observations suggest separate genetic pathways operating in race-specific and non-race-specific resistance; they indicate also a separate genetic control of hypersensitive and spontaneous cell death in foliar tissue.

Chauvet C, Bois-Joyeux B, Danan JL.Retinoic acid receptor-related orphan receptor (ROR) alpha4 is the predominant isoform of the nuclear receptor RORalpha in the liver

and is up-regulated by hypoxia in HepG2 human hepatoma cells.
**Biochem J. 2002 Jun 1;364(Pt 2):449-56.**
Centre de Recherche sur l'Endocrinologie Moleculaire et le Developpement, CNRS-UPR 9078, 9 rue Jules Hetzel, F92190 Meudon-Bellevue, France.

The retinoic acid receptor-related orphan receptor alpha (RORalpha) is critically involved in many physiological functions in several organs. We find that the main RORalpha isoform in the mouse liver is the RORalpha4 isoform, in terms of both mRNA and protein levels, while the RORalpha1 isoform is less abundant. Because hypoxia is a major feature of liver physiology and pathology, we examined the effect of this stress on Rora gene expression and RORalpha transcriptional activity. HepG2 human hepatoma cells were cultured for 24 h under normoxia (20% O2) or hypoxia (10, 2, and 0.1% O2) and the abundance of the Rora transcripts measured by Northern blot and semi-quantitative RT-PCR. Hypoxic HepG2 cells contained more Rora mRNA than controls. This was also observed in rat hepatocytes in primary culture. Cobalt chloride and desferrioxamine also increased the amount of Rora mRNA in HepG2 cells. It is likely that these treatments increase the amount of the RORalpha4 protein in HepG2 cells as evidenced by Western blotting in the case of desferrioxamine. Transient transfection experiments indicated that hypoxia, cobalt chloride, and desferrioxamine all stimulate RORalpha transcriptional activity in HepG2 cells. Hence, we believe that RORalpha participates in the control of gene transcription in hepatic cells and modulates gene expression in response to hypoxic stress.

Schultheiss H, Dechert C, Kogel KH, Huckelhoven R.
A small GTP-binding host protein is required for entry of powdery mildew fungus into epidermal cells of barley.
**Plant Physiol. 2002 Apr; 128(4):1447-54.**
Institute of Phytopathology and Applied Zoology, Justus-Liebig-University Giessen, Heinrich-Buff Ring 26-32, D-35392 Giessen, Germany.

Small GTP-binding proteins such as those from the RAC family are cytosolic signal transduction proteins that often are involved in processing of extracellular stimuli. Plant RAC proteins are implicated in regulation of plant cell architecture, secondary wall formation, meristem signaling, and defense against pathogens. We isolated a RacB homolog from barley (Hordeum vulgare) to study its role in resistance to the barley powdery mildew fungus (Blumeria graminis f.sp. hordei). RacB was constitutively expressed in the barley epidermis and its expression level was not strongly influenced by inoculation with B. graminis. However, after biolistic bombardment of barley leaf segments with RacB-double-stranded RNA, sequence-specific RNA interference with RacB function inhibited fungal haustorium establishment in a cell-autonomous and genotype-specific manner. Mutants compromised in function of the Mlo wild-type gene and the Ror1 gene (genotype mlo5 ror1) that are moderately susceptible to B. graminis showed no alteration in powdery mildew resistance upon RacB-specific RNA interference. Thus, the phenotype, induced by RacB-specific RNA interference, was apparently dependent on the same processes as mlo5-mediated broad resistance, which is

suppressed by ror1. We conclude that an RAC small GTP-binding protein is required for successful fungal haustorium establishment and that this function may be linked to MLO-associated functions.

Nomi M, Oishi I, Kani S, Suzuki H, Matsuda T, Yoda A, Kitamura M, Itoh K, Takeuchi S, Takeda K, Akira S, Ikeya M, Takada S, Minami Y.
Loss of mRor1 enhances the heart and skeletal abnormalities in mRor2-deficient mice: redundant and pleiotropic functions of mRor1 and mRor2 receptor tyrosine kinases.
**Mol Cell Biol. 2001 Dec; 21(24):8329-35.**
Department of Genome Sciences, Graduate School of Medicine, Kobe University, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan.

The mammalian Ror family of receptor tyrosine kinases consists of two structurally related proteins, Ror1 and Ror2. We have shown that mRor2-deficient mice exhibit widespread skeletal abnormalities, ventricular septal defects in the heart, and respiratory dysfunction, leading to neonatal lethality (S. Takeuchi, K. Takeda, I. Oishi, M. Nomi, M. Ikeya, K. Itoh, S. Tamura, T. Ueda, T. Hatta, H. Otani, T. Terashima, S. Takada, H. Yamamura, S. Akira, and Y. Minami, Genes Cells 5:71-78, 2000). Here we show that mRor1-deficient mice have no apparent skeletal or cardiac abnormalities, yet they also die soon after birth due to respiratory dysfunction. Interestingly, mRor1/mRor2 double mutant mice show markedly enhanced skeletal abnormalities compared with mRor2 mutant mice. Furthermore, double mutant mice also exhibit defects not observed in mRor2 mutant mice, including a sternal defect, dysplasia of the symphysis of the pubic bone, and complete transposition of the great arteries. These results indicate that mRor1 and mRor2 interact genetically in skeletal and cardiac development.

Sundvold H, Lien S.
Identification of a novel peroxisome proliferator-activated receptor (PPAR) gamma promoter in man and transactivation by the nuclear receptor RORalpha1.
**Biochem Biophys Res Commun. 2001 Sep 21;287(2):383-90.**
Department of Animal Science, Agricultural University of Norway, N-1432 Aas, Norway. hilde.sundvold@ihf.nlh.no

PPARgamma has been extensively studied for the past decade mainly due to its central role in promoting and maintaining the adipocyte phenotype. To date, three PPARgamma isoforms have been described in man. Here we show the presence of a fourth PPARgamma promoter with its cognate mRNA initiating at exon 1, as evidenced by primer extension analysis. The presence of a putative responsive element (RORE) for RORalpha, a representative of the ROR/RZR orphan receptor superfamily, in the novel promoter was investigated. By gelshift experiments and site-directed mutagenesis we show that this RORE specifically binds the RORalpha1 isoform. We further demonstrate that overexpression of RORalpha1, but not the RORalpha2 and RORalpha3 isoforms, induced a 40-fold increase in promoter activity in transient transfection assays in various cell lines. Considering the strong transcriptional activation it is likely that RORalpha1 forms a part of the multifactorial regulatory mechanisms that control expression of the human PPARgamma gene. 

Al-Shawi R, Ashton SV, Underwood C, Simons JP.Expression of the Ror1 and Ror2 receptor tyrosine kinase genes during mouse development.
**Dev Genes Evol. 2001 Apr; 211(4):161-71.**
Department of Anatomy and Developmental Biology, Royal Free and University College Medical School, University College London, Royal Free Campus, Rowland Hill Street, London, NW3 2PF, UK.

Ror1 and Ror2 are orphan receptor tyrosine kinases that are most closely related to MuSK and the Trk family of neurotrophin receptors. We report the results of an extensive in situ hybridisation survey of the expression of these genes during mouse development. Expression of Ror1 and Ror2 differs markedly at early stages (E8.5--E9.5). At these times, Ror2 is expressed much more widely than Ror1, expression of which is largely restricted to head mesenchyme. At later stages of development (E12.5--E14.5), Ror1 expression expands and Ror2 expression becomes more restricted than at earlier times, although expression of Ror1 continues to be more restricted than that of Ror2. These changes result in overlapping expression domains but with major differences remaining. In many cases Ror1 is expressed in a sub-set of Ror2-expressing tissues; in others, there is complementary expression of Ror1 and Ror2. Ror1 and Ror2 are both expressed in derivatives of all three germ layers and in most organ systems, including the nervous, circulatory, respiratory, digestive, urogenital and skeletal systems. Conspicuous themes are the expression in major sense organs, and in neural crest and its derivatives.

Matsuda T, Nomi M, Ikeya M, Kani S, Oishi I, Terashima T, Takada S, Minami Y.
Expression of the receptor tyrosine kinase genes, Ror1 and Ror2, during mouse development.
**Mech Dev. 2001 Jul; 105(1-2):153-6.**
Department of Biomedical Regulation, Kobe University, School of Medicine, 7-5-1, Kusunoki-cho, Chuo-ku, 650-0017, Kobe, Japan.

In mammals, the Ror-family receptor tyrosine kinases consist of two structurally related proteins, Ror1 and Ror2, characterized by the extracellular Frizzled-like cysteine-rich domain and membrane proximal kringle domains. As an attempt to gain insights into their roles in mouse development, expression patterns of Ror1 and Ror2 during early embryogenesis were examined and compared. Interestingly, at early stages, Ror1 and Ror2 exhibit similar expression patterns in the developing face, including the frontonasal process and pharyngeal arches, which are derived from cephalic neural crest cells. On the other hand, they exhibit different expression patterns in the developing limbs and brain, where the expression of Ror2 was detected broadly compared with that of Ror1. At a later stage, both genes are expressed in a similar fashion in the developing heart and lung, yet in a distinct manner in the brain and eye.

McKay SE, Hislop J, Scott D, Bulloch AG, Kaczmarek LK, Carew TJ, Sossin WS.
Aplysia ror forms clusters on the surface of identified neuroendocrine cells.
**Mol Cell Neurosci. 2001 May; 17(5):821-41.**

Department of Pharmacology, Yale University School of Medicine, New Haven, Connecticut 06520, USA.

The ror receptors are a highly conserved family of receptor tyrosine kinases genetically implicated in the establishment of cellular polarity. We have cloned a ror receptor from the marine mollusk Aplysia californica. Aplysia ror (Apror) is expressed in most developing neurons and some adult neuronal populations, including the neuroendocrine bag-cell neurons. The Apror protein is present in peripheral neuronal processes and ganglionic neuropil, implicating the kinase in the regulation of growth and/or synaptic events. In cultured bag-cell neurons, the majority of the protein is stored in intracellular organelles, whereas only a small fraction is expressed on the surface. When expressed on the cell surface, the protein is clustered on neurites, suggesting that Apror is involved in the organization of functional domains within neurons. Apror immunoreactivity partially colocalizes with the P-type calcium channel BC-alpha1A at bag-cell neuron varicosities, suggesting a role for Apror in organizing neuropeptide release sites. 

Roszmusz E, Patthy A, Trexler M, Patthy L.
Localization of disulfide bonds in the frizzled module of Ror1 receptor tyrosine kinase.
**J Biol Chem. 2001 May 25;276(21):18485-90.**
Institute of Enzymology, Biological Research Center, Hungarian Academy of Sciences, Budapest, P. O. Box 7, H-1518, Hungary.

The frizzled (FRZ) module is a novel module type that was first identified in G-protein-coupled receptors of the frizzled and smoothened families and has since been shown to be present in several secreted frizzled-related proteins, in some modular proteases, in collagen XVIII, and in various receptor tyrosine kinases of the Ror family. The FRZ modules constitute the extracellular ligand-binding region of frizzled receptors and are known to mediate signals of WNT family members through these receptors. With an eye toward defining the structure of this important module family, we have expressed the FRZ domain of rat Ror1 receptor tyrosine kinase in Pichia pastoris. By proteolytic digestion and amino acid sequencing the disulfide bonds were found to connect the 10 conserved cysteines in a 1-5, 2-4, 3-8, 6-10, and 7-9 pattern. Circular dichroism and differential scanning calorimetry studies on the recombinant protein indicate that the disulfide-bonded FRZ module corresponds to a single, compact, and remarkably stable folding domain possessing both alpha-helices and beta-strands.

Collins NC, Lahaye T, Peterhansel C, Freialdenhoven A, Corbitt M, Schulze-Lefert P.
Sequence haplotypes revealed by sequence-tagged site fine mapping of the Ror1 gene in the centromeric region of barley chromosome 1H.
**Plant Physiol. 2001 Mar; 125(3):1236-47.**
Sainsbury Laboratory, John Innes Centre, Colney Lane, Norwich, Norfolk NR4 7UH, United Kingdom.

We describe the development of polymerase chain reaction-based, sequence-tagged site (STS) markers for fine mapping of the barley (Hordeum vulgare) Ror1 gene required for broad-spectrum resistance to powdery mildew (Blumeria graminis f. sp. hordei). After locating Ror1 to the centromeric region of barley chromosome 1H using a combined amplified fragment length polymorphism/restriction fragment-length polymorphism (RFLP) approach, sequences of RFLP probes from this chromosome region of barley and corresponding genome regions from the related grass species oat (Avena spp.), wheat, and Triticum monococcum were used to develop STS markers. Primers based on the RFLP probe sequences were used to polymerase chain reaction-amplify and directly sequence homologous DNA stretches from each of four parents that were used for mapping. Over 28,000 bp from 22 markers were compared. In addition to one insertion/deletion of at least 2.0 kb, 79 small unique sequence polymorphisms were observed, including 65 single nucleotide substitutions, two dinucleotide substitutions, 11 insertion/deletions, and one 5-bp/10-bp exchange. The frequency of polymorphism between any two barley lines ranged from 0.9 to 3.0 kb, and was greatest for comparisons involving an Ethiopian landrace. Haplotype structure was observed in the marker sequences over distances of several hundred basepairs. Polymorphisms in 16 STSs were used to generate genetic markers, scored by restriction enzyme digestion or by direct sequencing. Over 2,300 segregants from three populations were used in Ror1 linkage analysis, mapping Ror1 to a 0.2- to 0.5-cM marker interval. We discuss the implications of sequence haplotypes and STS markers for the generation of high-density maps in cereals.

Gawlas K, Stunnenberg HG.
Differential binding and transcriptional behaviour of two highly related orphan receptors, ROR alpha(4) and ROR beta(1).
**Biochim Biophys Acta. 2000 Dec 1;1494(3):236-41.**
Department of Molecular Biology, University of Nijmegen, Toernooiveld 1, 6525 ED Nijmegen, The Netherlands.

Nuclear receptors are ligand-inducible transcription factors that can be classified into two major groups according to their DNA-binding properties. Members of the first group bind to DNA as dimers, either homo- or heterodimers; members of the second group are also able to bind as monomers. While the first group has been extensively studied biochemically, very little is known about nuclear receptors that bind and act as monomers. In this study, we compared the binding and transcriptional behaviour of ROR alpha (NR1F1) and ROR beta (NR1F2), two representatives of the subgroup of monomer-binding receptors. We show that although they are highly related in their amino acid structures, they display remarkably different binding behaviours. Furthermore, we provide evidence that ROR beta can efficiently activate transcription in vitro as a monomer.

Guerrero JM, Pozo D, Garcia-Maurino S, Carrillo A, Osuna C, Molinero P, Calvo JR.
Nuclear receptors are involved in the enhanced IL-6 production by melatonin in U937 cells.
**Biol Signals Recept. 2000 May-Aug; 9(3-4):197-202.**

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This report shows that melatonin enhances IL-6 production by U937 cells via a nuclear receptor-mediated mechanism. Resting U937 cells only express membrane (mt1) melatonin receptors. In these cells, melatonin did not modify basal production of IL-6 or when activated by PMA plus lipopolysaccharide, a treatment that downregulates the expression of mt1 receptor. However, in U937 cells activated with IFN-gamma, which induces the expression of the ROR alpha 1 and ROR alpha 2 nuclear receptors and represses the expression of the mt1 receptor, melatonin can activate IL-6 production. These results show that the expression of nuclear melatonin receptor but not membrane receptors is sufficient for melatonin to activate cytokine production in human lymphocytic and monocytic cell lines. 

Chu K, Zingg HH.
Activation of the mouse oxytocin promoter by the orphan receptor RORalpha.
**J Mol Endocrinol. 1999 Dec; 23(3):337-46.**

Laboratory of Molecular Endocrinology, Royal Victoria Hospital Research Institute, McGill University, Montreal, Quebec, Canada H3A 1A1.

Although an increasing number of nuclear orphan receptors have recently been identified, the number of known naturally occurring genes that are directly regulated by orphan receptors is still small. We have shown previously that the gene encoding the neuropeptide oxytocin (OT) is negatively regulated by the orphan receptors chicken ovalbumin upstream transcription factor I (COUP-TFI) and II. Here we show that the mouse OT gene promoter is activated by RORalpha, a representative of the ROR/RZR orphan receptor subfamily. Using promoter/chloramphenicol acetyltransferase reporter constructs in heterologous transfection assays, we determined that RORalpha action induces a <6-fold increase in promoter activity. By 5' and 3' deletion analysis, DNase footprint analysis and electrophoretic mobility shift assays, we found that RORalpha action is mediated by two 14 bp regions centered at 160 and 180 nucleotides upstream of the transcriptional initiation site. Both sites contain significant sequence identities with an established ROR recognition sequence. Mutations in either or both of these sites reduce significantly RORalpha-induced activation of the OT promoter. In view of the strong transcriptional activation exerted by RORalpha on the OT gene promoter and the widespread distribution of different members of the ROR/RZR family, interactions between ROR/RZR isoforms and the OT gene may form part of the multifactorial regulatory mechanisms that control OT gene expression in different tissues.

Oishi I, Takeuchi S, Hashimoto R, Nagabukuro A, Ueda T, Liu ZJ, Hatta T, Akira S, Matsuda Y, Yamamura H, Otani H, Minami Y.
Spatio-temporally regulated expression of receptor tyrosine kinases, mRor1, mRor2, during mouse development: implications in development and function of the nervous

system.
**Genes Cells. 1999 Jan; 4(1):41-56.**
Department of Biochemistry, Kobe University, School of Medicine, 7-5-1, Kusunoki-cho, Chuo-ku, Kobe 650, Japan.

BACKGROUNDS: Drosophila neurospecific receptor tyrosine kinases (RTKs), Dror and Dnrk, as well as Ror1 and Ror2 RTKs, isolated from human neuroblastoma, have been identified as a structurally related novel family of RTKs (Ror-family RTKs). Thus far, little is known about the expression and function of mammalian Ror-family RTKs. RESULTS: We have identified murine Ror-family RTKs, mRor1 and mRor2. Both mRor1 and mRor2 genes are induced upon neuronal differentiation of P19EC cells. During neuronal differentiation in vitro, the expression of mRor2 is transiently induced, although that of mRor1 increases continuously. During embryogenesis, the mRor1 gene is expressed in the developing nervous system within restricted regions and in the developing lens epithelium. The expression of mRor1 is sustained in the nervous system and is also detected in non-neuronal tissues after birth. In contrast, the expression of mRor2 is detected mainly in the developing nervous system within broader regions and declines after birth. Possible relationships of mRor1 and mRor2 genes with previously identified mutants have also been examined. CONCLUSIONS: The developmental expressions of mRor1 and mRor2, in particular in the nervous system, are differentially regulated, reflecting their expression patterns in vitro. mRor1 and mRor2 may thus play differential roles during the development of the nervous system.

Saldanha J, Singh J, Mahadevan D.
Identification of a Frizzled-like cysteine rich domain in the extracellular region of developmental receptor tyrosine kinases.
**Protein Sci. 1998 Aug; 7(8):1632-5.**
Division of Mathematical Biology, National Institute for Medical Research, London, United Kingdom.

In Drosophila, members of the Frizzled family of tissue-polarity genes encode proteins that appear to function as cell-surface receptors for Wnts. The Frizzled genes belong to the seven transmembrane class of receptors (7TMR) and have on their extracellular region a cysteine-rich domain that has been implicated as the Wnt binding domain. This region has a characteristic spacing of ten cysteines, which has also been identified in FrzB (a secreted antagonist of Wnt signaling) and Smoothened (another 7TMR, which is involved in the hedgehog signalling pathway). We have identified, using BLAST, sequence similarity between the cysteine-rich domain of Frizzled and several receptor tyrosine kinases, which have roles in development. These include the muscle-specific receptor tyrosine kinase (MuSK), the neuronal specific kinase (NSK2), and ROR1 and ROR2. At present, the ligands for these developmental tyrosine kinases are unknown. Our results suggest that Wnt-like ligands may bind to these developmental tyrosine kinases

Lau P, Bailey P, Dowhan DH, Muscat GE.
Exogenous expression of a dominant negative RORalpha1 vector in muscle cells impairs differentiation: RORalpha1 directly interacts with p300 and myoD.
Nucleic Acids Res. 1999 Jan 15;27(2):411-20.
University of Queensland, Centre for Molecular and Cellular Biology, Ritchie Research Laboratories, B402A, St Lucia, 4072, Queensland, Australia.
ROR/RZR is an orphan nuclear receptor that has no known ligand in the 'classical sense'. In the present study we demonstrate that RORalpha is constitutively expressed during the differentiation of proliferating myoblasts to post-mitotic multinucleated myotubes, that have acquired a contractile phenotype. Exogenous expression of dominant negative RORalpha1DeltaE mRNA in myogenic cells significantly reduces the endogenous expression of RORalpha1 mRNA, represses the accumu-lation and delays the activation of mRNAs encoding MyoD and myogenin [the muscle-specific basic helix-loop-helix (bHLH) proteins] and p21(Waf-1/Cip-1) (a cdk inhibitor). Immunohistochemistry demonstrates that morpho-logical differentiation is delayed in cells expressing the RORDeltaE transcript. Furthermore, the size and development of mutlinucleated myotubes is impaired. The E region of RORalpha1 interacts with p300, a cofactor that functions as a coactivator in nuclear receptor and MyoD-mediated transactivation. Consistent with the functional role of RORalpha1 in myogenesis, we observed that RORalpha1 directly interacts with the bHLH protein MyoD. This interaction was mediated by the N-terminal activation domain of the bHLH protein, MyoD, and the RORalpha1 DNA binding domain/C region. Furthermore, we demonstrated that p300, RORalpha1 and MyoD interact in a non-competitive manner. In conclusion, this study provides evidence for a biological role and positive influence of RORalpha1 in the cascade of events involved in the activation of myogenic-specific markers and cell cycle regulators and suggests that crosstalk between theretinoid-relatedorphan (ROR) nuclear receptors and the myogenic bHLH proteins has functional consequences for differentiation.

Saldanha J, Singh J, Mahadevan D.
Identification of a Frizzled-like cysteine rich domain in the extracellular region of developmental receptor tyrosine kinases.
**Protein Sci. 1998 Jul; 7(7):1632-5.**
Division of Mathematical Biology, National Institute for Medical Research, London, United Kingdom.

In Drosophila, members of the Frizzled family of tissue-polarity genes encode proteins that appear to function as cell-surface receptors for Wnts. The Frizzled genes belong to the seven transmembrane class of receptors (7TMR) and have on their extracellular region a cysteine-rich domain that has been implicated as the Wnt binding domain. This region has a characteristic spacing of ten cysteines, which has also been identified in FrzB (a secreted antagonist of Wnt signaling) and Smoothened (another 7TMR, which is involved in suppression of the hedgehog pathway). We have identified, using BLAST, sequence similarity between the cysteine-rich domain of Frizzled and several receptor tyrosine kinases, which have roles in development. These include the muscle-specific receptor tyrosine kinase (MuSK), the neuronal specific kinase (NSK2), and ROR1 and ROR2. At present, the ligands for these developmental tyrosine kinases are unknown.

Our results suggest that Wnt-like ligands may bind to these developmental tyrosine kinases.

Matysiak-Scholze U, Nehls M.
The structural integrity of ROR alpha isoforms is mutated in staggerer mice: cerebellar coexpression of ROR alpha1 and ROR alpha4.
**Genomics. 1997 Jul 1;43(1):78-84.**
German Cancer Research Center (DKFZ), Heidelberg.

The recessive mouse mutation staggerer (sg) disturbs the normal development of cerebellar Purkinje cells and affects certain functions of the immune system. To identify the causative gene, we constructed high-resolution genetic and physical maps of the staggerer locus on mouse chromosome 9. The transcription unit of the orphan nuclear receptor ROR alpha was identified in the critical interval. Our mutational analysis confirms a recent report that the sg phenotype may be caused by a genomic deletion in the common coding region of the ROR alpha isoforms. Of the four different isoforms of the ROR alpha gene that are generated by a combination of alternative promoter usage and exon splicing that differ in their DNA-binding properties, isoforms ROR alpha1 and ROR alpha4 are specifically coexpressed in the murine cerebellum and human cerebellum. Thus, at least two isoforms of the murine ROR alpha gene are affected by the genomic deletion associated with the staggerer phenotype. Our finding of cerebellum-specific coregulation suggests that distinct sets of target genes regulated by the ROR alpha1 and ROR alpha4 isoforms are required for Purkinje cell development.

Oishi I, Sugiyama S, Liu ZJ, Yamamura H, Nishida Y, Minami Y.
A novel Drosophila receptor tyrosine kinase expressed specifically in the nervous system. Unique structural features and implication in developmental signaling.
**J Biol Chem. 1997 May 2;272(18):11916-23.**
Department of Biochemistry, Kobe University School of Medicine, 7-5-1, Kusunoki-chou, Chuo-Ku, Kobe 650, Japan.

We report the identification and characterization of Dnrk (Drosophila neurospecific receptor kinase), a Drosophila gene encoding a putative receptor tyrosine kinase (RTK) highly related to the Trk and Ror families of RTKs. During Drosophila embryogenesis, the Dnrk gene is expressed specifically in the developing nervous system. The Dnrk protein possesses two conserved cysteine-containing domains and a kringle domain within its extracellular domain, resembling those observed in Ror family RTKs (Ror1, Ror2, and a Drosophila Ror, Dror). This protein contains the catalytic tyrosine kinase (TK) domain with two putative ATP-binding motifs, resembling those observed in another Drosophila RTK (Dtrk) that mediates homophilic cell adhesion. The TK domain of Dnrk, expressed in bacteria or mammalian cells, exhibits apparent autophosphorylation activities in vitro. The TK domain lacking the distal ATP-binding motif also exhibits autophosphorylation activity, yet to a lesser extent. In addition to its TK activity, there are several putative tyrosine-containing motifs that upon phosphorylation may interact with Src homology 2 regions of other signaling molecules. Collectively, these results

suggest that Dnrk may play an important role in neural development during Drosophila embryogenesis.

Reddy UR, Phatak S, Allen C, Nycum LM, Sulman EP, White PS, Biegel JA.
Localization of the human Ror1 gene (NTRKR1) to chromosome 1p31-p32 by fluorescence in situ hybridization and somatic cell hybrid analysis.
**Genomics. 1997 Apr 15;41(2):283-5.**
Division of Neurology Research, Children's Hospital of Philadelphia, Pennsylvania 19104, USA. reddyu@mail.med.u-penn.edu

Ror1 is an orphan cell surface receptor with strong homology to the tyrosine kinase domain of growth factor receptors, in particular the Trk family. Southern blot analysis of genomic DNA from somatic cell hybrids revealed that Ror1 is located on chromosome 1. We have mapped the Ror1 gene to chromosome 1p12-p32 using PCR on a somatic cell hybrid panel that subdivides chromosome 1p. We have further localized the gene to chromosome 1p31-p32 by fluorescence in situ hybridization using a PAC clone that contains the Ror1 gene.

Reddy UR, Phatak S, Pleasure D.
Human neural tissues express a truncated Ror1 receptor tyrosine kinase, lacking both extracellular and transmembrane domains.
**Oncogene. 1996 Oct 3;13(7):1555-9.**
Division of Neurology Research, The Children's Hospital of Philadelphia, Pennsylvania 19104, USA.

Human heart, lung and kidney express a 6 kb mRNA encoding Ror1, a member of the receptor tyrosine kinase (RTK) family with as yet unknown ligand specificity. We used a Ror1 cDNA probe to screen a cDNA library prepared from the human neuronogenic teratocarcinoma line, NTera2, and cloned a 2373 nucleotide transcript. This transcript contains an open reading frame that encodes a 388 amino acid protein identical with the cytosolic, C-terminal region of ror1 but lacking the ror1 transmembrane and entire extracellular domains. Northern blots demonstrate that mRNA encoding this truncated Ror1 ('t-Ror1') is abundantly expressed in fetal and adult human CNS, in human leukemia, lymphoma cell lines, and in a variety of human cancers derived from neuroectoderm. While previous studies have documented alternative splicing patterns within 5' and 3' regions of mRNAs encoding various RTKs altering their ligand binding specificity or their intracellular signaling, the present report is the first to demonstrate tissue-specific alternative mRNA splicing causing loss of the entire extracellular and transmembrane regions of an RTK.

Carlberg C, Wiesenberg I.
The orphan receptor family RZR/ROR, melatonin and 5-lipoxygenase: an unexpected relationship.
**J Pineal Res. 1995 May; 18(4):171-8. Review.**

Clinique de Dermatologie, Hopital Cantonal Universitaire, Geneva, Switzerland.
The orphan receptors RZR alpha, RZR beta, ROR alpha 1, RZR alpha 2, ROR alpha 3, and ROR gamma form a subfamily within the superfamily of nuclear hormone receptors. Recently, experimental evidence that the pineal gland hormone melatonin is the natural ligand for these nuclear receptors has come to light. This discovery is rather surprising, given that most people in the field believed melatonin acts exclusively through membrane receptors. However, these new findings establish a nuclear signalling pathway for melatonin, i.e., direct ligand-induced control of target gene transcription, which most probably mediates part of the physiological functions of the hormone. Interestingly, the very recently identified first RZR/melatonin responding gene, 5-lipoxygenase, is not expressed in the brain and is not involved in circadian rhythmicity, but rather acts in the periphery, mainly in myeloid cells, as one of the key enzymes of allergic and inflammatory reactions. Thus, nuclear melatonin signalling opens up a new perspective in understanding the actions of the pineal gland hormone.

McBroom LD, Flock G, Giguere V.
The nonconserved hinge region and distinct amino-terminal domains of the ROR alpha orphan nuclear receptor isoforms are required for proper DNA bending and ROR alpha-DNA interactions.
**Mol Cell Biol. 1995 Feb; 15(2):796-808.**
Department of Biochemistry, McGill University, Royal Victoria Hospital, Montreal, Quebec, Canada.

ROR alpha 1 and ROR alpha 2 are two isoforms of a novel member of the steroid-thyroid-retinoid receptor superfamily and are considered orphan receptors since their cognate ligand has yet to be identified. These putative receptors have previously been shown to bind as monomers to a DNA recognition sequence composed of two distinct moieties, a 3' nuclear receptor core half-site AGGTCA preceded by a 5' AT-rich sequence. Recognition of this bipartite hormone response element (RORE) requires both the zinc-binding motifs and a group of amino acid residues located at the carboxy-terminal end of the DNA-binding domain (DBD) which is referred to here as the carboxy-terminal extension. In this report, we show that binding of ROR alpha 1 and ROR alpha 2 to the RORE induces a large DNA bend of approximately 130 degrees which may be important for receptor function. The overall direction of the DNA bend is towards the major groove at the center of the 3' AGGTCA half-site. The presence of the nonconserved hinge region which is located between the DBD and the putative ligand-binding domain (LBD) or ROR alpha is required for maximal DNA bending. Deletion of a large portion of the amino-terminal domain (NTD) of the ROR alpha protein does not alter the DNA bend angle but shifts the DNA bend center 5' relative to the bend induced by intact ROR alpha. Methylation interference studies using the NTD-deleted ROR alpha 1 mutant indicate that some DNA contacts in the 5' AT-rich half of the RORE are also shifted 5', while those in the 3' AGGTCA half-site are unaffected. These results are consistent with a model in which the ROR alpha NTD and the nonconserved hinge region orient the zinc-binding motifs and the carboxy-terminal extension of the ROR alpha DBD relative to each other to achieve proper interactions with the two halves of its recognition

site. Transactivation studies suggest that both protein-induced DNA bending and protein-protein interactions are important for receptor function.

Forman BM, Chen J, Blumberg B, Kliewer SA, Henshaw R, Ong ES, Evans RM.
Cross-talk among ROR alpha 1 and the Rev-erb family of orphan nuclear receptors.
**Mol Endocrinol. 1994 Sep; 8(9):1253-61.**
Salk Institute for Biological Studies, Gene Expression Laboratory, San Diego, California 92186-5800.

We have cloned Rev-erb beta, a novel isoform of the Rev-erb alpha orphan nuclear receptor. The DNA binding domains of Rev-erb alpha and beta are highly related to each other and to the retinoic acid related orphan receptor (ROR)/RZR subfamily of nuclear receptors. Indeed, we find that all three receptors bind as monomers to the sequence AATGT-AGGTCA. Whereas ROR alpha 1 constitutively activates transcription through this sequence, both isoforms of Rev-erb are inactive. When coexpressed, both Rev-erb isoforms suppress the transcriptional activity of ROR alpha 1. Our data define Rev-erb and ROR/RZR as a family of related receptors with opposing activities on overlapping regulatory networks.

Wilson C, Goberdhan DC, Steller H.
Dror, a potential neurotrophic receptor gene, encodes a Drosophila homolog of the vertebrate Ror family of Trk-related receptor tyrosine kinases.
**Proc Natl Acad Sci U S A. 1993 Aug 1;90(15):7109-13.**
Howard Hughes Medical Institute, Department of Biology, Massachusetts Institute of Technology, Cambridge 02139.

We have identified a Drosophila gene, Dror, which encodes a putative receptor tyrosine kinase (RTK) and maps to cytological location 31B/C on the second chromosome. In embryos, this gene is expressed specifically in the developing nervous system. The Dror protein appears to be a homolog of two human RTKs, Ror1 and Ror2. Dror and Ror1 proteins share 36% amino acid identity in their extracellular domains and 61% identity in their catalytic tyrosine kinase (TK) domains. Ror1 and Ror2 were originally identified on the basis of the similarity of their TK domains to the TK domains of members of the Trk family of neurotrophin receptors. The Dror protein shows even greater similarity to the Trk proteins within this region than do the human Ror proteins. In light of its similarity to trk and its neural-specific expression pattern, we suggest that Dror may encode a neurotrophic receptor that functions during early stages of neural development in Drosophila.

Masiakowski P, Carroll RD.
A novel family of cell surface receptors with tyrosine kinase-like domain.
**J Biol Chem. 1992 Dec 25;267(36):26181-90.**
Regeneron Pharmaceuticals, Tarrytown, New York 10591-6707.

Human cDNA clones encoding two novel proteins with a region strongly homologous to

the tyrosine kinase domain of growth factor receptors, in particular of the Trk family, were obtained by a polymerase chain reaction-based approach. These proteins, Ror1 and Ror2, share 58% overall amino acid identity and a structure indicative of cell surface molecules. A secretion signal sequence and a transmembrane domain delimit the extracellular portion, which contains immunoglobulin-like, cysteine-rich, and kringle domains. The cytoplasmic portion contains the tyrosine kinase-like domain which (in Ror2) appears to be associated with protein kinase activity in vitro, followed by serine/threonine- and proline-rich motifs. Partial nucleotide sequences of the rat genes reveal striking evolutionary conservation of the proteins between human and rat. The level of expression of the rat genes is high in the head and body of early embryo and decreases dramatically after embryonic day 16. Based on these data, Ror1 and Ror2 appear to define a new developmentally regulated family of cell surface receptors for unidentified ligands.